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VIETNAM - FRANCE - ASIA - PACIFIC
CONFERENCE ON OBSTETRICS AND GYNECOLOGY
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16th

# Implementation of NIPT in Vietnam

# PROSPECTS AND CHALLENGES

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# The burden of birth defects and genetics diseases

**Increasing**

- 30% of hospitalized diseases in children
- 20% neonatal mortality &50% child mortality
- > 50% miscarriages before 13 gestation weeks

**Difficult, costly treatment, poor quality of life**

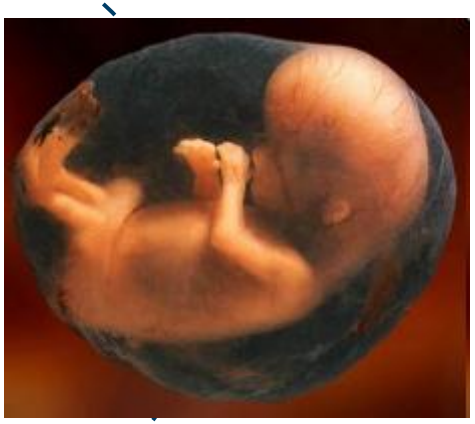
*(Prenat Neonat Med 1999;4:157-164)*



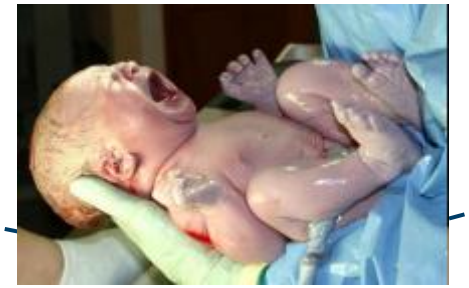

# Prevent genetics disorders

PGD

PMD

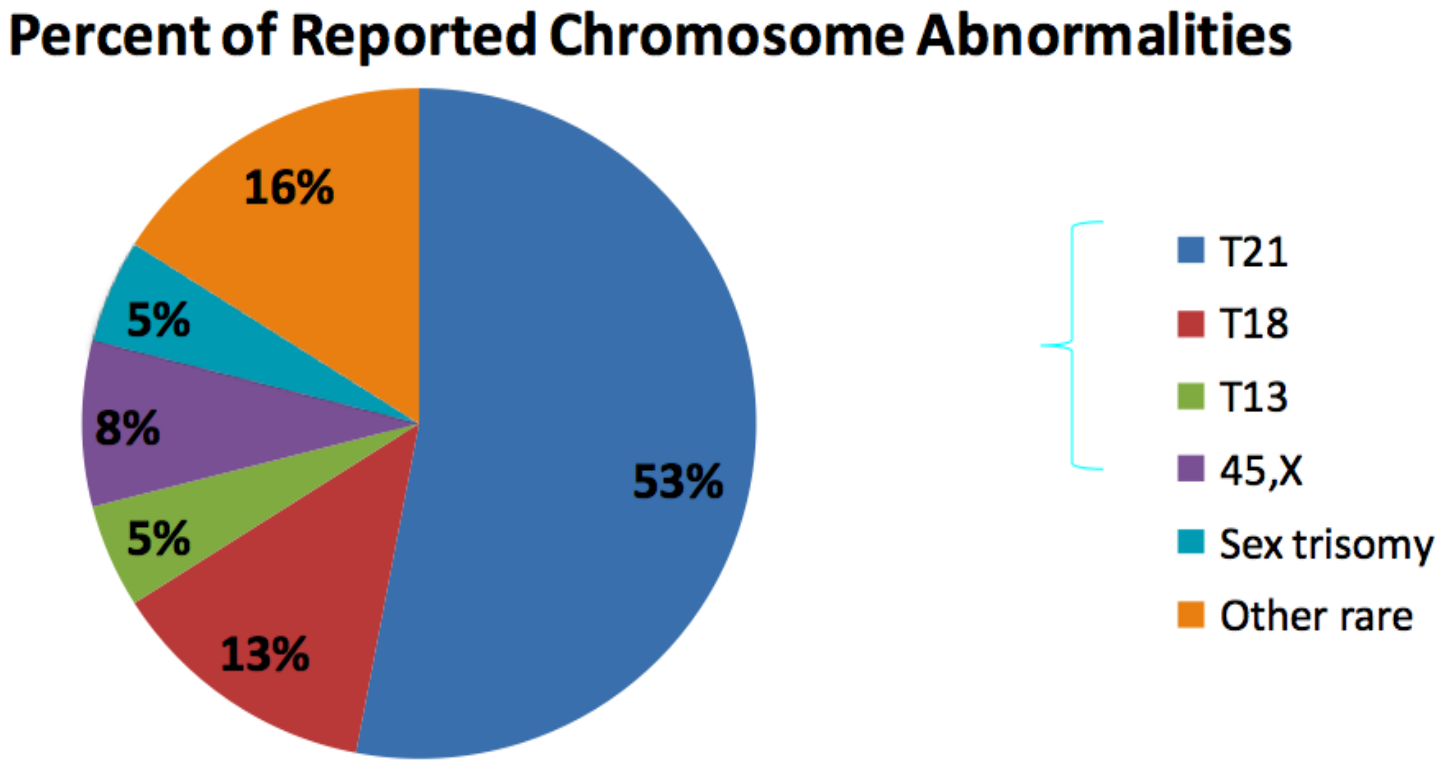


PND



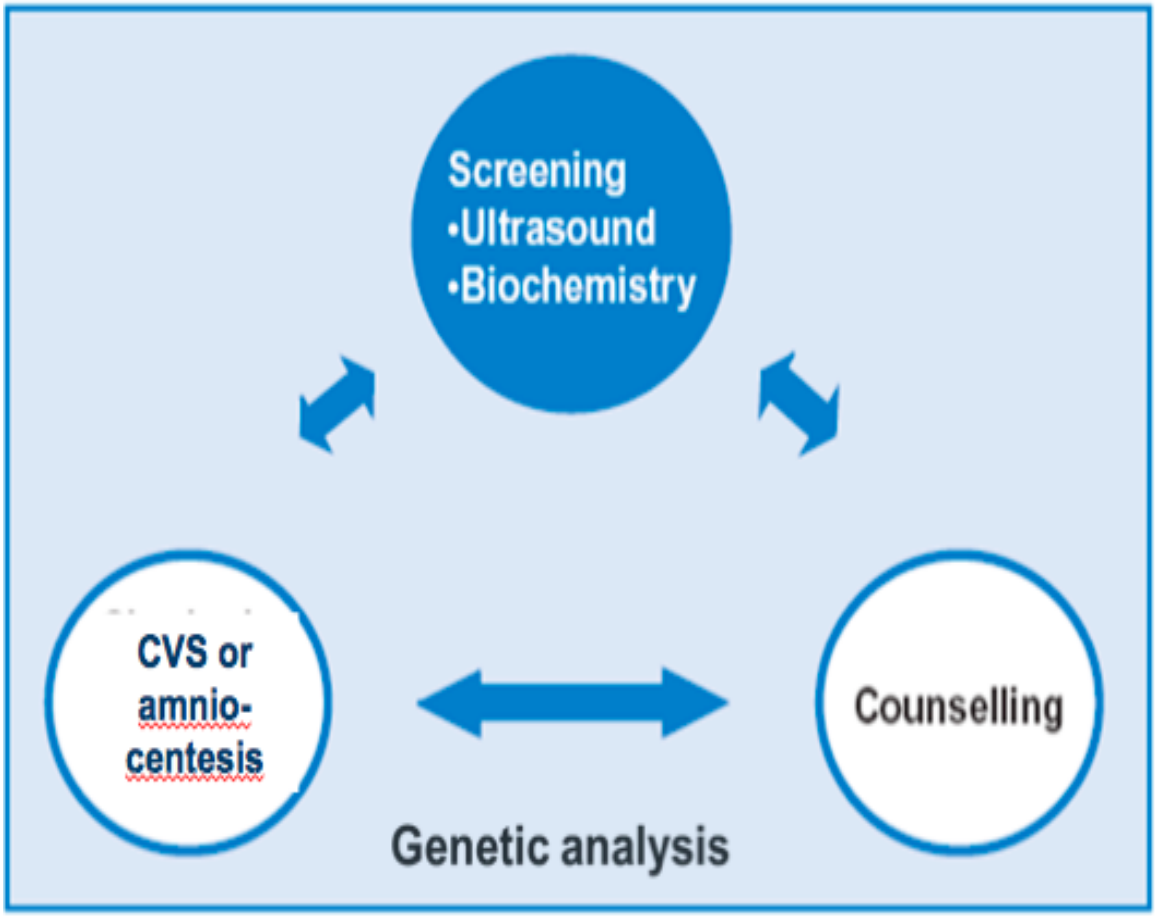
NBD

# Prenatal prevalence of chromosomal abnormalities



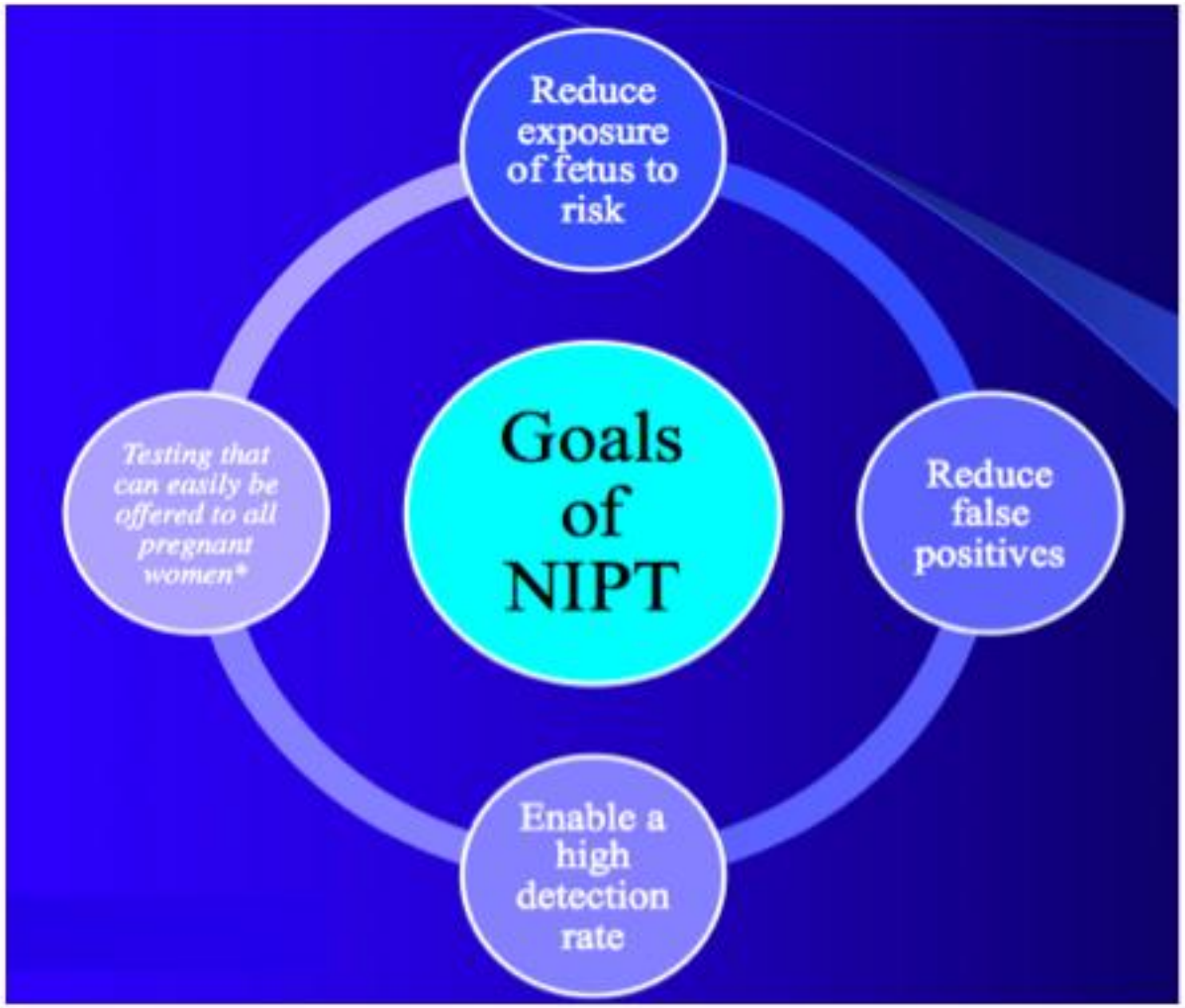

Data adapted from Wellesley, D, et al., Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. *Eur J of Hum Gen*, 11 January 2012.

# Current prenatal screen and diagnosis

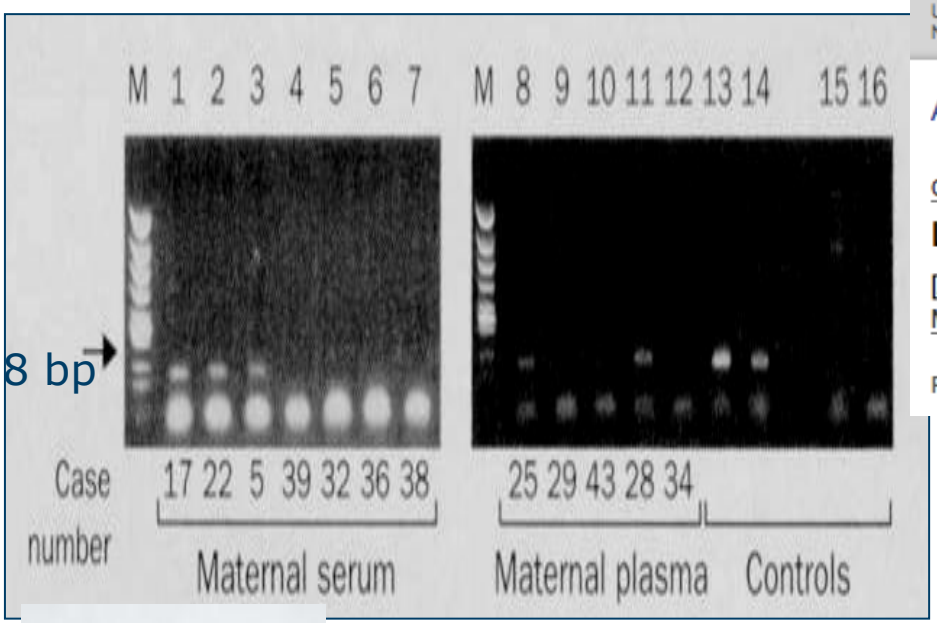



- Detection rate: ≤94%
- False possitive: 5%
- Not screen sex chromosomal disorders
- Fetal losses due to invasive test: 0,2-1%

# 2010's: NIPT/NIPS



# Technology behind NIPT: cell free fetal DNA




PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

C R Seances Soc Biol Fil. 1948 Feb;142(3-4):241-3.

**Les acides nucléiques du plasma sanguin chez l'homme.**

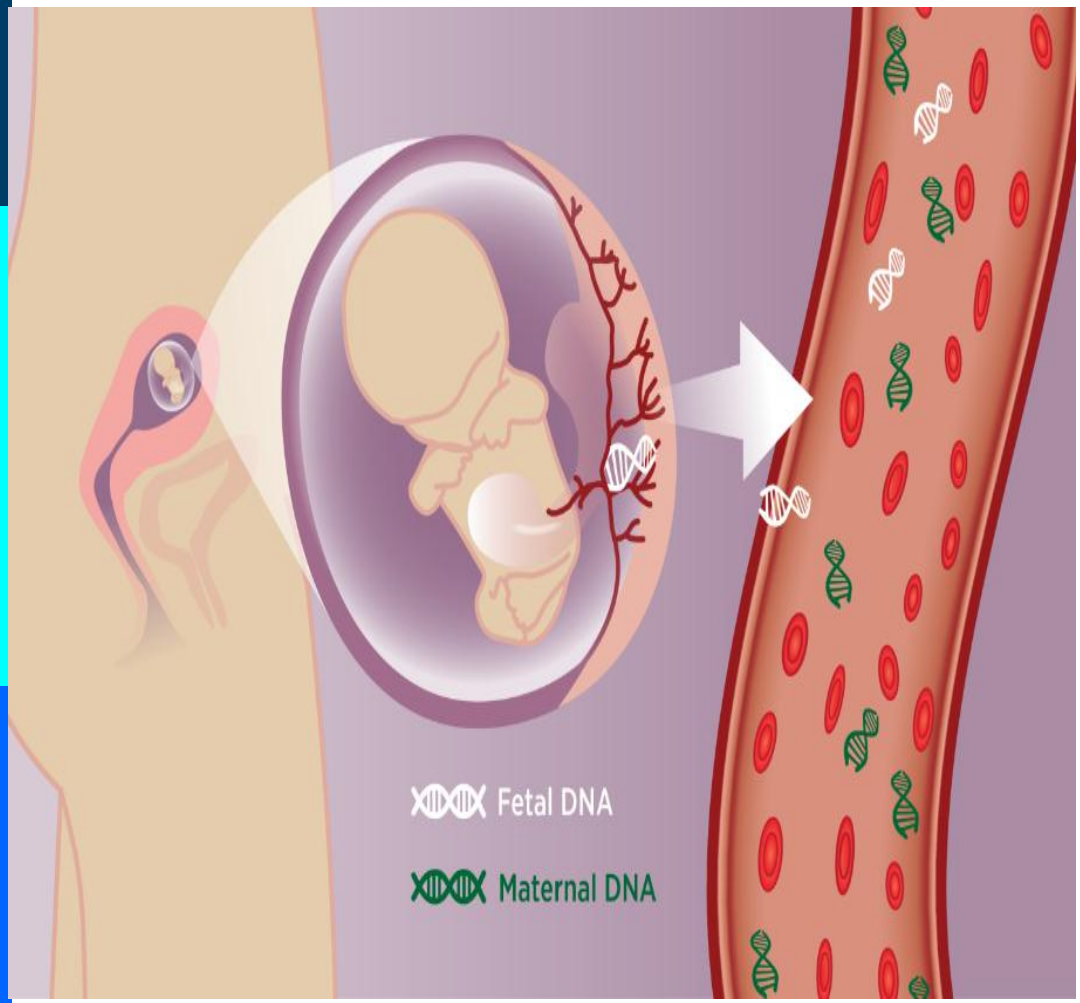
[Article in Undetermined Language]
MANDEL P, METAIS P.

PMID: 18875018 [PubMed - indexed for MEDLINE]

10. Mandel P, Métais P. Les acides nucleiques du plasma sanguin chez l'homme. C R Seances Soc Biol Fil. 1948;143:241–3.

Lo et al. *Lancet* 1997; 350:485

# cffDNA in maternal plasma




- Short DNA: 150-340 bp
- Source: almost from placenta cells, a litle from fetal blood cells..
- Increasing with pregnancy : 3-19%
- Haft - life: 16.3 minutes
- Undetectable within 2 hours postpartum

# History of NIPT

- 1997: Lo et al. : finding fetus-derived Y sequences inmaternal plasma from women bearing male fetuses
- 2001 : diagnosing Rh(D) genotype
- 2006 : diagnosing seks chromosome
    - X link diseases (DMD, Hemophilia…)
    - Gender

➔ Based on the principle of PCR: limited specificity, sensitivity

➔ Applied in detecting chromosomal abnormalities: taking time, labour, missinformation…

# Advent of Next Generation Sequencing (NGS)

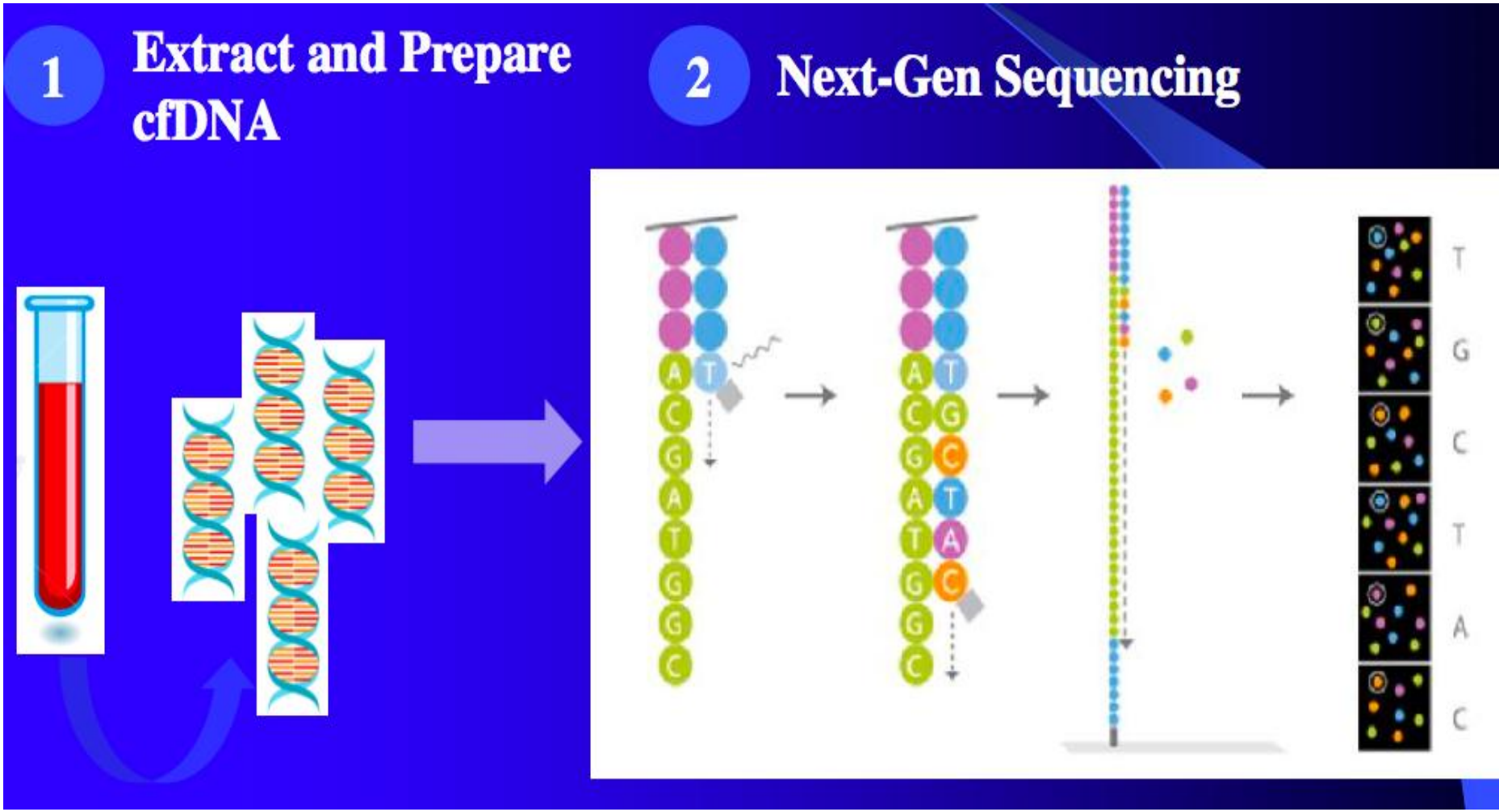
Sequencing millions – 43 billions short DNA fragments/time

- ➔ Simplify diagnosis of genetics diseases
- ➔ 2011: NIPT was introduced

**2008 detection of Trisomy 21**

- **Chiu RW, Chan KC, Gao Y, et al. Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. Proc Natl Acad Sci USA 2008;105:20458-20463**
- **Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. Proc Natl Acad Sci USA 2008;105:16266-16271**

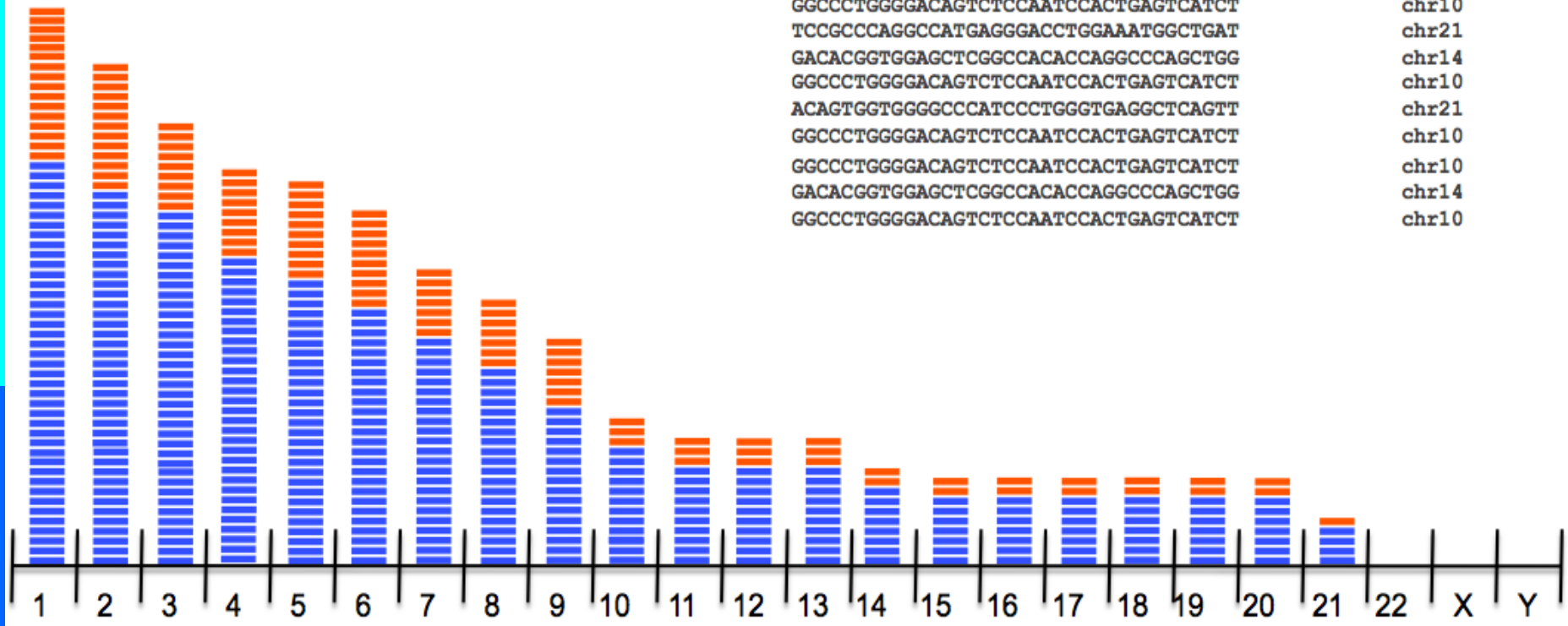
# NGS and NIPT



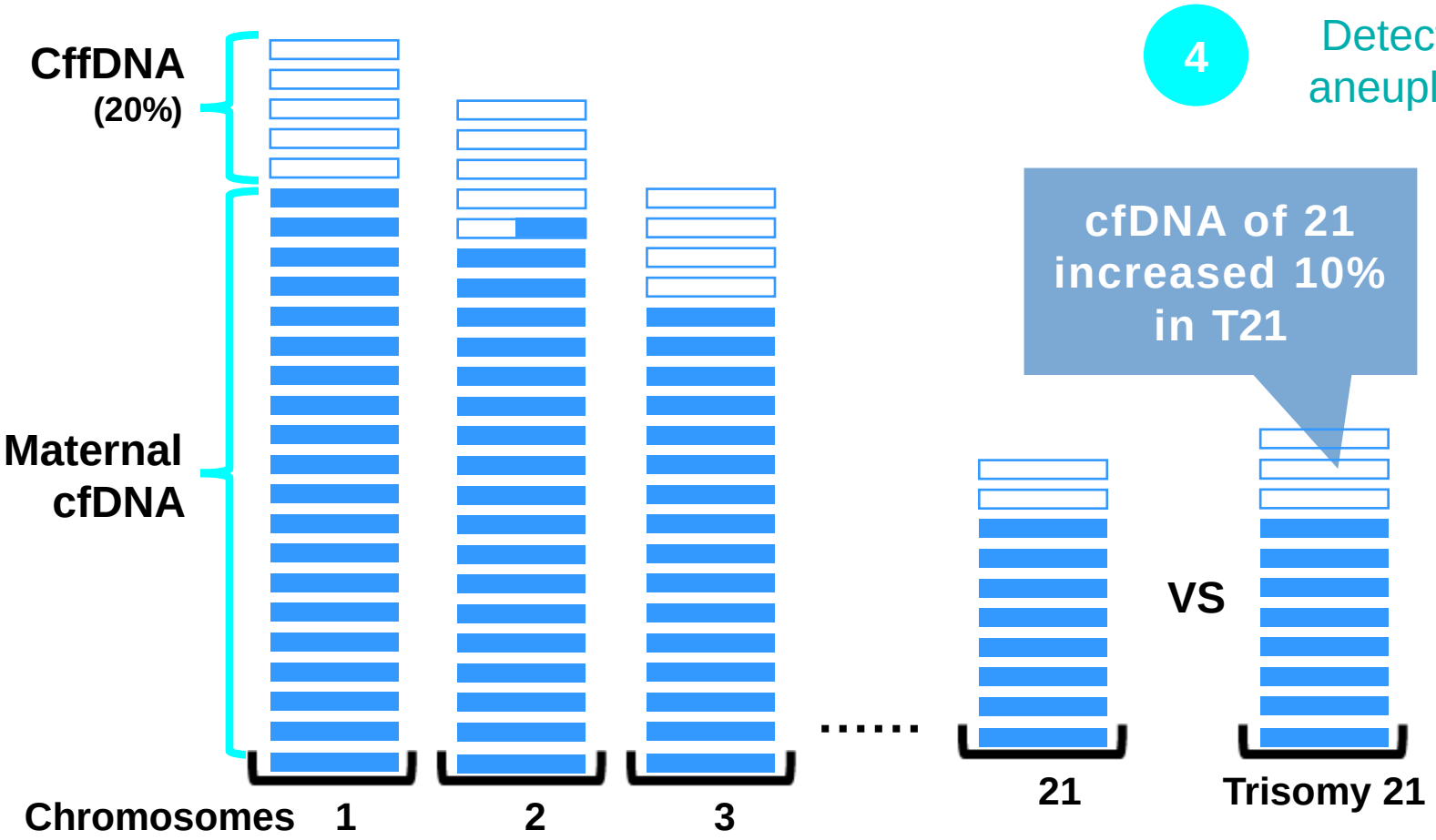
# NGS and NIPT: aligment and map

Sequencing tells you which chromosome the ccf fragment comes from

| | |
|---|---|
| TCCGCCCAGGCCATGAGGGACCTGGAAATGGCTGAT | chr21 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG | chr14 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| ACAGTGGTGGGGCCCATCCCTGGGTGAGGCTCAGTT | chr21 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| TCCGCCCAGGCCATGAGGGACCTGGAAATGGCTGAT | chr21 |
| GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG | chr14 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| ACAGTGGTGGGGCCCATCCCTGGGTGAGGCTCAGTT | chr21 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |
| GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG | chr14 |
| GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT | chr10 |



# NGS/NIPT: analyse, count copies of chromosomes



ULTRASOUND
in Obstetrics & Gynecology

isuog

*Ultrasound Obstet Gynecol* 2015; 45: 249–266
Published online 1 February 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.14791

# Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis

- 37 relevant studies 2011-2015
- 5 had data from the general population
- Most were retrospective or prospective

# Meta analysis of NIPT (n=21.608)

| ANEUPLOIDY | NUMBER | DR (%) | FP(%) |
|---|---|---|---|
| Trisomy 21 | 1.051 | 99,2 | 0,09 |
| Trisomy 18 | 389 | 96,3 | 0,13 |
| Trisomy 13 | 139 | 91 | 0,13 |
| Monosomy X | 177 | 90,3 | 0,23 |
| Others | 56 | 93 | 0,14 |
| Trisomy 21 (twin) | | 93,7 | 0,23 |

Gil M.M. Ultrasound Obstet Gynecol 2015

# Meta analysis of NIPT

**Table 1.** Cell-free DNA Test Performance Characteristics in Patients Who Receive an Interpretable Result*

| | | | Age 25 years | Age 40 years |
|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | PPV (%) | PPV (%) |
| Trisomy 21 | 99.3 | 99.8 | 33 | 87 |
| Trisomy 18 | 97.4 | 99.8 | 13 | 68 |
| Trisomy 13 | 91.6 | 99.9 | 9 | 57 |
| Sex chromosome aneuploidy | 91.0 | 99.6 | --[†] | -- |

*(ACOG committee opinion, No.640, sep 2015)*

# NIPT: DS/Miscarriage due to Invasive test

| | DR | FPR | DS /CVS (risk 1/100) | DS/Amniocentesis ( risk 1/500) |
|---|---|---|---|---|
| Combined test 1st | 90% | 5% | 5:2 | 13:1 |
| Triple test 2nd | 70% | 5% | | 10:1 |
| NIPT | 99,3% | 0,16% | 90:1 | 444:1 |
| | 99,8% | 0.05% | 180:1 | 1400:1 |

T21: 1/700

. ACOG Practice Bulletin No. 77, January 2007
. Benn et al, Ultras Obstet Gynecol 2013, 42: 15-33

# ACOG Committee Opinion on NIPT


- *"Cell free fetal DNA appears to be the most effective screening test for aneuploidy in high risk women… is one option that can be used as a primary screening test in women at increased risk of aneuploidy"*
- *"[NIPT] should be an informed patient choice after pretest counseling"*
- *"[NIPT] should not be offered to low-risk women or women with multiple gestations"*
- *"A patient with a positive test result should be referred for genetic counseling and should be offered invasive prenatal diagnosis for confirmation of test results."*

**Also supporting NIPT for high risk pregnancies:**

ispd

National Society of Genetic Counselors

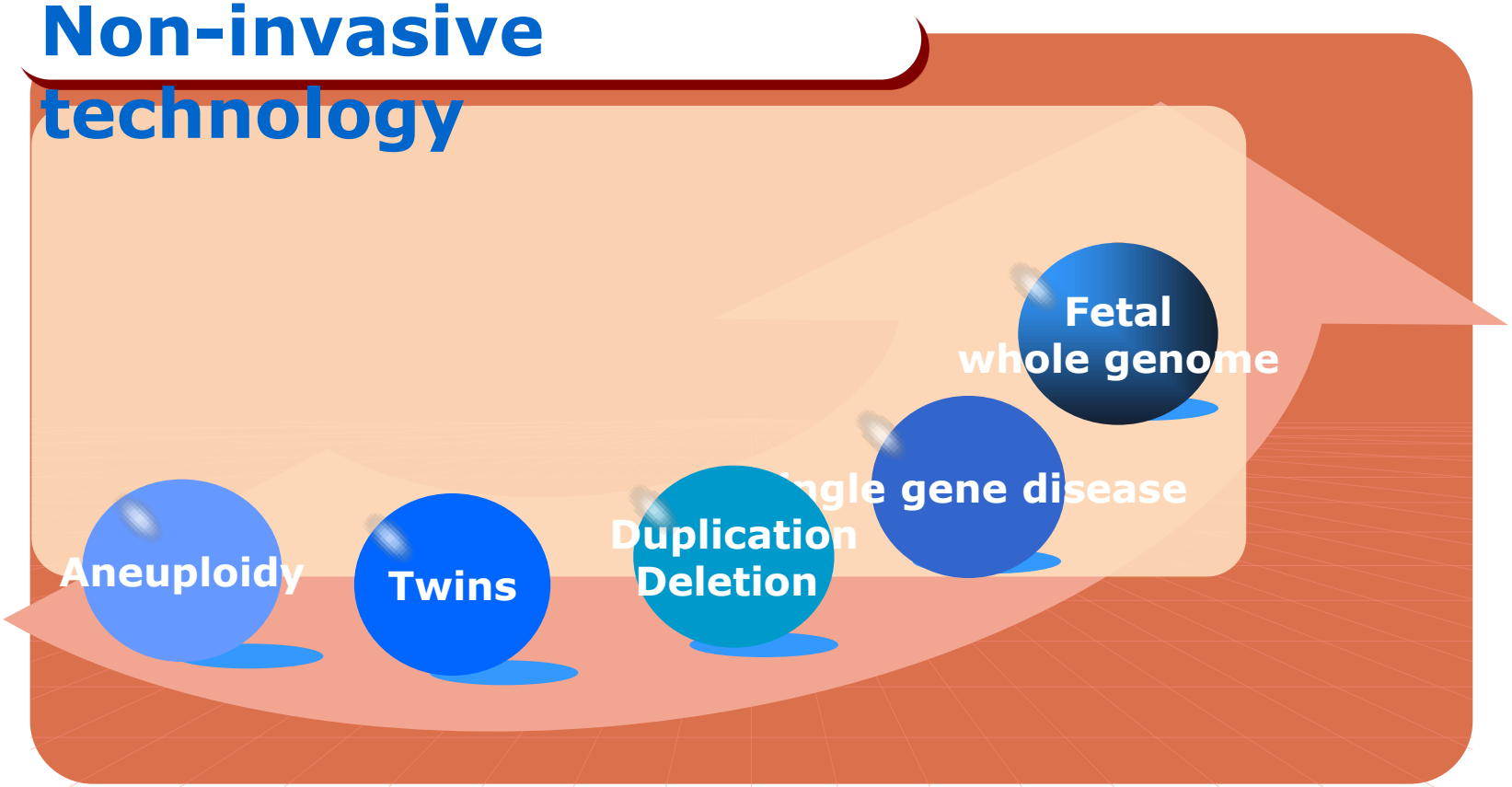
Consensus with high-risk pregnancies

# NIPT: limitations

- High cost
- For low risk, twin, microdeletion pregnancies, single gen test…: Not yet recommendation
- Discordant results:
  - Confined placenta mosaicism
  - Fetal mosaicism
  - Vanishing twin
  - Maternal abnormal karyotype
  - Discordant twin
  - Cancer

# Prospect of NIPT

## Non-invasive technology




J. Cao 2014

# NIPT in Vietnam

verifi

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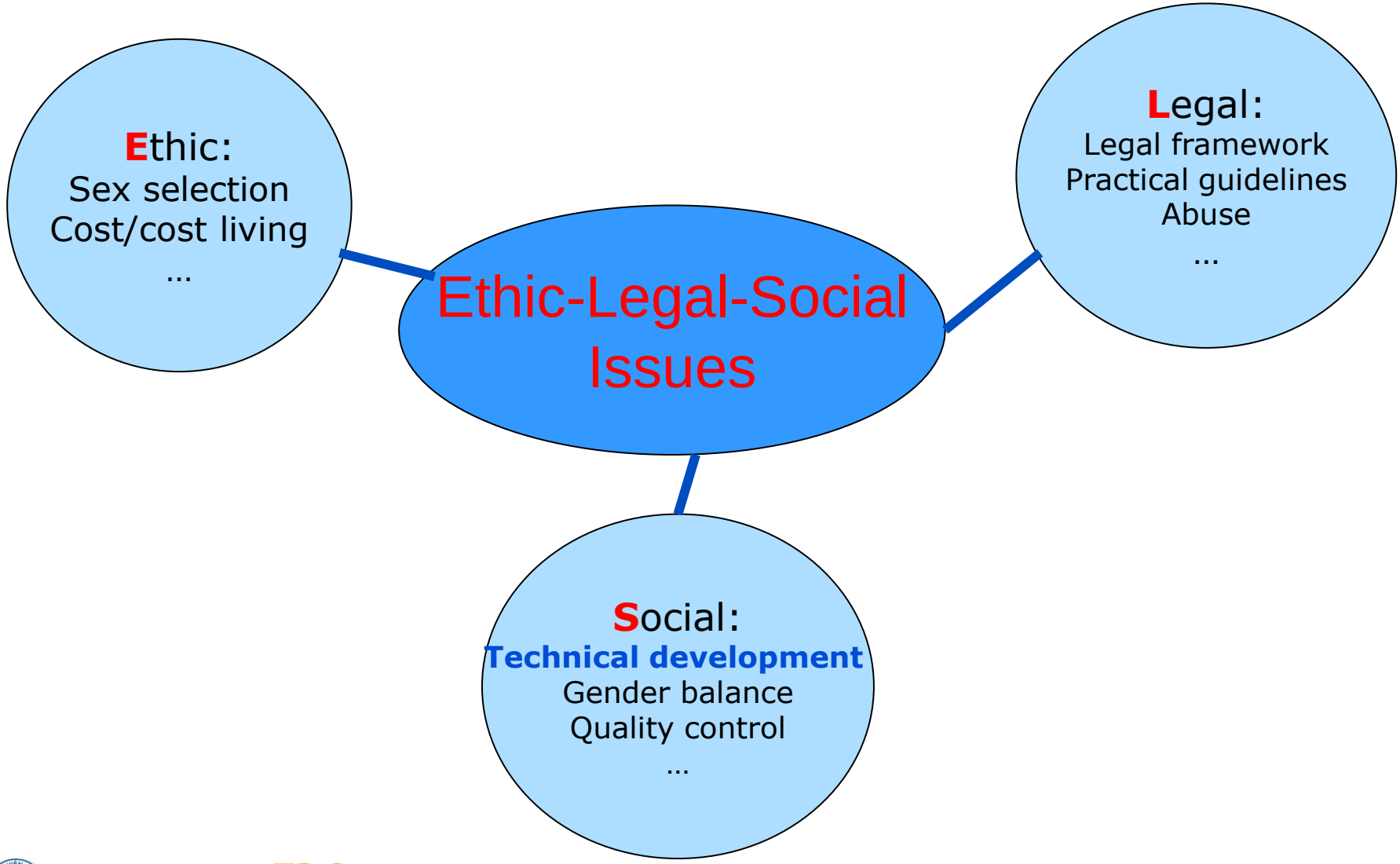
Ariosa™

BerryGenomics
贝瑞和康

华大基因
BGI

- Pregnant women have the opportunity to reach new advances
- Interpreting results:
  - Consistent with Trisomy – Disomy
  - Affected – Unaffected
  - High risk – low risk
  - Possitive – Negative
  - Aneuploidy suspected
  - PPV, residual risk value: ±

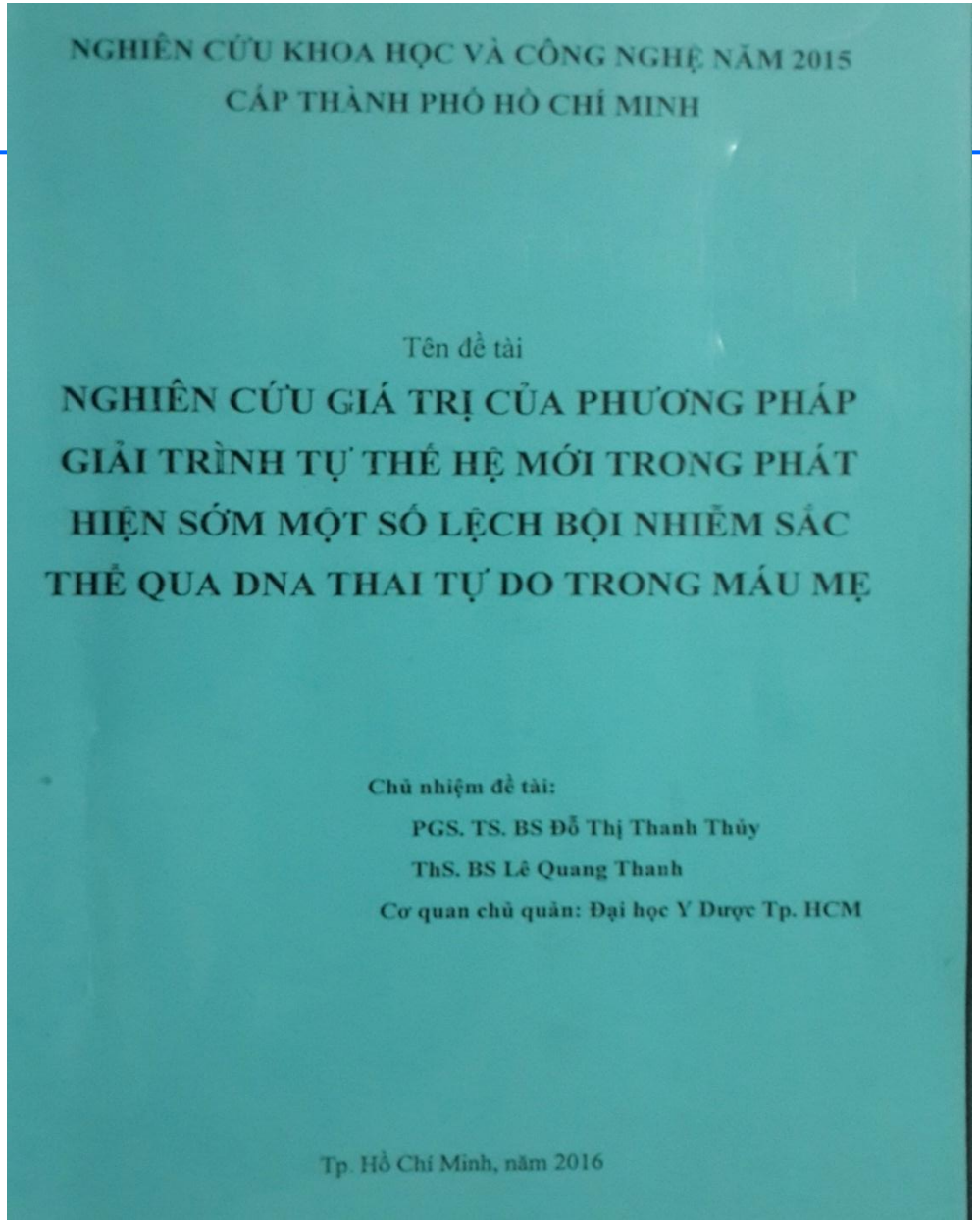
# NIPT in Vietnam



# Apply cffDNA in Vietnam

- Detecting cffDNA in maternal plasma by PCR and applying in prenatal diagnosis of genetics
  (Trinh Tien Sang et al., 2013, Vietnam Medical Journal)
- NGS technology: new, undeveloping
- Bioinformatic: undeveloping
- Research about NIPT: Not yet

Feb/2016



NGHIÊN CỨU KHOA HỌC VÀ CÔNG NGHỆ NĂM 2015
CẤP THÀNH PHỐ HỒ CHÍ MINH

Tên đề tài

# NGHIÊN CỨU GIÁ TRỊ CỦA PHƯƠNG PHÁP GIẢI TRÌNH TỰ THẾ HỆ MỚI TRONG PHÁT HIỆN SỚM MỘT SỐ LỆCH BỘI NHIỄM SẮC THỂ QUA DNA THAI TỰ DO TRONG MÁU MẸ

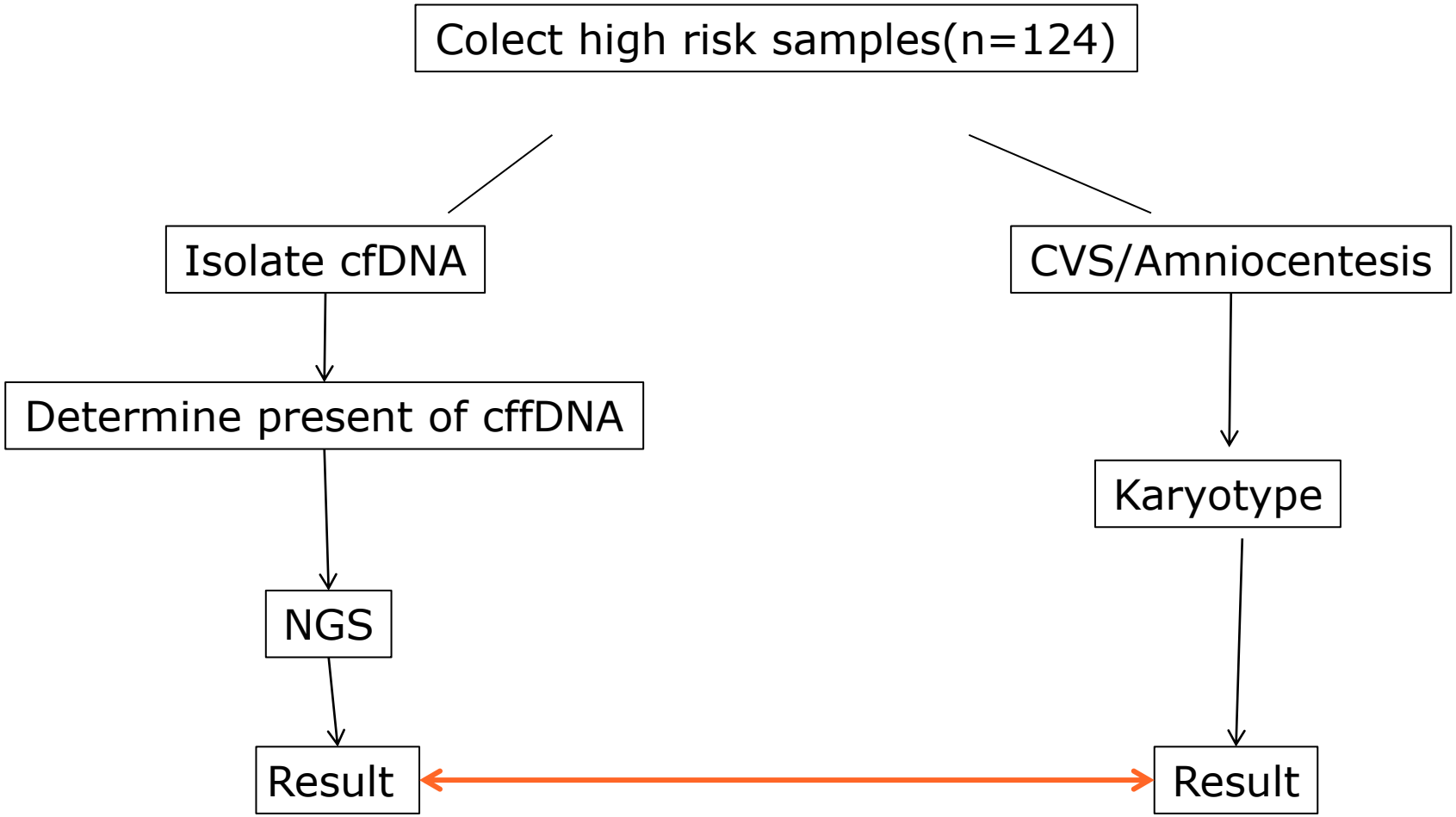
**Chủ nhiệm đề tài:**
PGS. TS. BS Đỗ Thị Thanh Thủy
ThS. BS Lê Quang Thanh
**Cơ quan chủ quản: Đại học Y Dược Tp. HCM**

Tp. Hồ Chí Minh, năm 2016

# ➢ Objectives

- Setting up the protocol for isolating cfDNA from maternal blood and determining the present of cffDNA in it
- Determining values (sensitivity, specificity, NPV, PPV) of NGS in detecting aneuploidies by cffDNA in maternal plasma

# Processing flow



# CONCLUSION

- NIPT: Inevitable trend in prenatal screening and diagnosis
- Implementation of NIPT in Vietnam: many challenges about ethics, social, legal, technique…
- Need to promote researches about the applications of cffDNA to make legal framework, clinical practical guidelines NIPT in Vietnam.


Thank you!